Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The SONIC HEDGEHOG ("SHH")-signalling pathway regulates epithelial-mesenchymal interactions during the development of many organs. SHH protein is synthesised in epithelial cells, and in many situations, acts as a paracrine factor through its receptor PATCHED1 ("PTC") that is expressed in adjacent mesenchymal cells. Disruption of SHH-signalling has provided evidence for important and diverse roles in organogenesis. *Shh* knockout mice exhibit various developmental defects, including cyclopia, neural tube defects and absence of distal limb structures. Inhibition of SHH-signalling using cyclopamine (Cy) has further demonstrated the role of SHH-signalling in development of the neural tube, gastro-intestinal tract, pancreas, and in hair follicle morphogenesis. SHH-signalling is also required for branching morphogenesis of the lung. *Shh* transcript expression has been reported in the urogenital sinus ("UGS") epithelium where it is required for the formation of external genitalia, and might play an important role in prostate development.

Prostate organogenesis is an androgen-dependent process that involves reciprocal signalling between the epithelium and mesenchyme, but little is known about the molecular mediators that control these epithelial-mesenchymal interactions. *Shh* is expressed in the UGS epithelium, and its importance in prostate growth was demonstrated by antibody blockade of SHH, which abrogated growth of the prostate from male UGS tissue transplanted into male host mice. Podlasek et al also reported that *Shh* transcript expression was upregulated in males in response to androgens, concluding that androgen-induced expression of *Shh* in the UGS is necessary for prostatic induction. However, BMP4, a putative downstream signalling effector of the SHH-signalling pathway, is expressed in the UGS mesenchyme independent of androgen action. This discrepancy raised the possibility that androgens might not regulate *Shh* in the growing prostate, prompting us to re-examine this in detail. We have addressed the role of SHH-signalling in prostate organogenesis, by detailed examination of *Shh* and *Ptc* transcript expression, and by disrupting the SHH-signalling pathway in ventral prostate (VPs) grown in vitro.

The data presented in the present application suggest *Shh* and *Ptc* transcript expression is not dependent on androgens, and that SHH-signalling is required for VP growth. Furthermore, the presented data also demonstrates that inhibition of SHH-signalling during VP growth effects epithelial growth, patterning and differentiation, and results in prostatic epithelial ducts reminiscent of human cribiform prostatic intraepithelial neoplasia (PIN).

Although treatments for inhibition of SHH signalling pathway were known previously and treatments for decreasing production of androgens or causing their effects to be removed (i.e., androgen blockade) were known previously, prior to the present invention there was no suggestion that the latter treatments can be used in the combination with the former to protect a male patient from possible adverse effects on the prostate caused by treatments involving inhibition of the SHH-signalling pathway. This includes use of the combination therapy during treatment of a male patient for a proliferative disease that involves inhibiting the SHH-signalling (e.g., the treatment of cancers in which SHH-signalling plays a role in its growth and/or differentiation).

The present application describes for the first time that in the use of compounds that inhibit the SHH signalling pathway for medical treatment of male patients, it is important for androgens or their effects to be removed.

Request for Reconsideration of Species Election

Given the nature of the invention (as described above and as claimed), applicant respectfully requests withdrawal of the election of species requirement. Moreover, it appears that the U.S. Patent and Trademark Office ("PTO") has already considered the patentability of subject matter outside the scope of the elected subject matter. Indeed, on page 6 of the outstanding office action, the PTO has asserted that the specification is enabling for "ameliorating the basal cell carcinoma and suppressing the effects of testosterone in patients with glioblastoma, and regulating prostatic growth *in vitro*…." In making this statement, it is evident that the PTO has necessarily considered the patentability of subject matter outside the scope of the elected species. Therefore, applicant respectfully requests withdrawal of the election of species requirement either in its entirety or at least with respect to the proliferative disorders.

Claim Amendments

By the above claim amendments, claims 1, 2, 3, 5, 8, 24, and 26 have been amended, and claims 6, 7, and 27-29 have been canceled without prejudice. Claims 1-5, 8, 18, 19, 21, and 24-26 remain pending.

Claims 1 and 2 recite that the patient is a male patient, which is supported by previously presented claim 6 (now canceled), and claim 2 recites that "the proliferative disease is a cancer in which SHH-signalling plays a role in its growth and/or differentiation, and the cancer is not prostate cancer," which is supported by previously presented claim 7 (now canceled) and the description in the written specification of cancers in which SHH-signalling plays a role (*see* page 13, line 28, to page 14, line 7). In addition, claim 1 has been amended to indicate that the adverse effects are "on the prostate," which is supported in the application at page 3, lines 7 to 10. Claim 24 has been amended to clarify that the treatment involving inhibition of the SHH-signalling pathway includes "administration of cyclopamine or a derivative thereof to the male patient." No new matter has been introduced by these amendments.

Claims reading on the elected species include claims 1, 18, 19, 21, and 24-26. For the reasons noted above, however, applicant respectfully requests withdrawal of the election of species requirement and examination of all presently pending claims.

Specification Amendments

The specification has been amended to comply with preferred PTO organization. In addition, a typographical error at page 8, line 8, has been corrected. The cited U.S. patent is elsewhere correctly identified (*see* page 4, line 17), therefore no new matter is introduced by these amendments.

All objections to the Title and Specification should be withdrawn.

Responses to Claim Rejections

The rejection of claims 1 and 24-29 under 35 U.S.C. §112, second paragraph, for indefiniteness is respectfully traversed in view of the above amendments.

Claim 1 has been amended to indicate that the adverse effect is "on the prostate." Plainly, this language cannot include such things as rashes, sore muscles, dry mouths, headaches, etc. Therefore, this basis of rejection is overcome.

Applicant respectfully submits that the objection to the lack of antecedent basis is improper. Claim 1 recites in the preamble the phrase "a treatment involving

inhibition of the SHH-signalling pathway in the patient." This language makes clear that it is the SHH-signaling pathway *in the patient* that is being inhibited. It is implicit that the patient possesses such a pathway and, therefore, there is no need to require modification of the claim language.

Claim 24 has been amended to clarify that it is the administration of cyclopamine which inhibits the SHH-signalling pathway. Claim 24 is now perfectly clear in the context of limiting claim 1, because it is cyclopamine which inhibits the SHH-signalling pathway and it is the suppression of testosterone that protects the male patient against the possible adverse effects of the SHH-signalling pathway inhibitor (i.e., cyclopamine) on the prostate.

In view of the foregoing, the rejection of claims 1 and 24-29 under 35 U.S.C. §112, second paragraph, should be withdrawn.

The rejection of claims 1-8, 18, 19, 21, and 24-29 under 35 U.S.C. § 112, first paragraph, for lack of enablement is respectfully traversed.

As discussed above, the presently claimed invention relates to a method of protecting a male patient from possible adverse effects on the prostate that may be caused by a treatment involving inhibition of the SHH-signalling pathway (claim 1) and a method of treating a proliferative disease in a male patient that involves: inhibiting the SHH-signalling pathway and suppressing testosterone or its effect in the patient, wherein the proliferative disease is a cancer in which SHH-signalling plays a role in its growth and/or differentiation, and the cancer is not prostate cancer (claim 2). Thus, the invention relates to the combination of (i) treatments for inhibition of SHH-signalling pathway and (ii) treatments for decreasing production of androgens or causing their effects to be removed (i.e., androgen blockade).

On page 6 of the outstanding office action, the PTO correctly considers that the specification is enabling for ameliorating basal cell carcinoma and suppressing the effects of testosterone in patients with glioblastoma and regulating prostatic growth *in vitro*. However, the PTO goes on to assert that the specification does not reasonably provide enablement for treating all proliferative diseases *in vivo*. Applicant disagrees for the following reasons.

Claims 1 and 2 are restricted to male patients who are receiving treatment with an SHH-signalling pathway inhibitor, and claim 2 is also restricted to cancers—other

than prostate cancer—in which SHH-signalling plays a role in its growth and/or differentiation.

The patent specification provides details of the known treatments of various diseases with SHH-signalling pathway inhibitors (*see* page 3, line 12 to page 4, line 18), and page 5, line 14 to page 8, line 18 provides details of known SHH-signalling pathway inhibitors. Thus, there is plainly an enabling disclosure of the treatment of patients with SHH-signalling pathway inhibitors. That step of the combination therapy is plainly within the scope of the prior art.

In addition, methods of suppressing testosterone are well known in the art. The patent specification clearly describes ways of suppressing testosterone, see in particular page 12, line 22 to page 14, line 19.

Because treatments of various diseases with SHH-signalling pathway inhibitors were known in the art and treatments for suppressing testosterone were known in the art, there can be no lack of enablement in combining these previously known treatments. (Because the adverse effect on the prostate caused by treatment with SHH-signalling pathway inhibitors was not previously known, for the reasons discussed below the claimed invention is both novel and inventive.)

For these reasons, the rejection of claims 1-8, 18, 19, 21, and 24-29 under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

The rejection of claims 1 and 25-29 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,925,619 to Walsh *et al.* ("Walsh") is respectfully traversed. Walsh merely relates to formulations and administration of GnRH analogues, particularly the peptide deslorelin. Walsh addresses the need to suppress testosterone or estradiol levels for the treatment of a number of conditions/diseases, including prostate cancer, ovarian and breast cancer, benign hormone-dependent disorders such as endometriosis, myoma, and premenstrual tension, and precocious puberty in children (Walsh at col. 3, line 64 to col. 4, line 4). Walsh does *not* mention or suggest in any way that suppression of testosterone should be carried out in combination with a treatment that involves inhibition of the SHH-signalling pathway. In particular, Walsh fails to teach or suggest suppressing testosterone to protect a male patient from possible adverse effects on the prostate caused by the treatment involving inhibition of the SHH-signalling pathway. For this reason, the rejection of claims 1 and 25-29 as anticipated by Walsh is improper and should be withdrawn.

The rejection of claims 1, 24, 25, and 27-29 under 35 U.S.C. § 102(b) as anticipated by WO 02/030462 to Dudek *et al* ("Dudek I") is respectfully traversed.

Dudek I relates to regulators of the SHH-signalling pathway and their use in treating various conditions. There is no disclosure or suggestion of using regulators of the SHH-signalling pathway in conjunction with the suppression of testosterone.

In making this rejection, the PTO has made several erroneous assertions at page 20 of the office action. In particular, the PTO asserts as follows:

> Furthermore, the reference discloses that recent evidence supporting the essential role of SHH in proper prostate branching demonstrates that treatment of embryonic prostate with hedgehog antagonist cyclopamine inhibits growth and branching (see p. 174, lines 4-9). This meets the limitation of claims 1, 24-25 and 27-29.

Office Action (dated June 8, 2007) at 20, lines 2-6; and

> Since the reference disclose [sic] the same claimed disease to be treated, the same claimed active agent, the disclosed method of using GnRH agonist cyclopamine would inherently suppress testosterone levels to castrate levels.

Office Action (dated June 8, 2007) at 20, lines 6-9.

Applicant respectfully disagrees with both of these assertions. With respect to the first assertion, there is no mention in Dudek I of suppressing testosterone or its effect in the male patient as recited in claim 1. Because Dudek I fails to teach or suggest this feature of the claimed invention, Dudek I cannot be construed in any way to satisfy the limitations of claim 1 or claims 24, 25, and 27-29 dependent thereon. With respect to the second assertion, Dudek I in no way supports the assertion that cyclopamine is a GnRH agonist. Cyclopamine is a SHH signalling pathway inhibitor (*see* page 7, lines 24-26 of the present application; *see also* Dudek I at p. 93, lines 19-21 (identifying cyclopamine as "hedgehog antagonist"). Thus, cyclopamine is *not* a GnRH agonist, it does *not* suppress testosterone, and there is no portion of Dudek I that can be cited for even the suggestion of suppressing testosterone or its effect in the patient.

Because Dudek I fails to teach or suggest each and every limitation of the claimed invention, the rejection of claims 1, 24, 25, and 27-29 as anticipated by Dudek I is improper and should be withdrawn.

The rejection of claims 1 and 24-29 under 35 U.S.C. § 103(a) for obviousness over Dudek I in view of Walsh is respectfully traversed.

The teachings and deficiencies of Dudek I and Walsh are noted above.

The PTO asserts at page 22 of the outstanding office action that the claimed invention would have been obvious, because (i) Dudek I teaches using cyclopamine for inhibiting growth and branching of prostate cancer, (ii) Walsh teaches the use of deslorelin for treatment of prostate and breast cancer, and (iii) the combining of two components for a known purpose would have been expected to produce additive effects.

Applicant respectfully disagrees for several reasons.

Firstly, the invention of claims 1 and 24-29 relates to a method of protecting a male patient from possible adverse effects on the prostate that are caused by a treatment involving inhibition of the SHH-signalling pathway in the patient. There is no suggestion in Dudek I that inhibitors of the SHH-signalling pathway cause adverse effects on the prostate when testosterone is present. Therefore, there is no motivation whatsoever from Dudek I to suppress testosterone, and so the skilled person would not have considered combining Dudek I with Walsh.

Secondly, the fundamental premise cited by the PTO at pages 22-23—that the claimed combination is used for the same purpose—is improper. As noted above, the invention of claim 1 relates to therapeutic methods of treating male patients to avoid possible adverse effects caused by a treatment involving inhibition of the SHH-signalling pathway. Thus, suppressing testosterone or its effect in the male patient, i.e., via a GnRH agonist, is not being used for "the same purpose" but instead for a biologically distinct purpose. Rather than administering a GnRH agonist to treat prostate cancer, the GnRH agonist is used to avoid possible adverse effects caused by a treatment involving inhibition of the SHH-signalling pathway (whether or not that is used to effect a treatment for prostate cancer). This is a distinct effect that is neither taught nor suggested in the cited art.

Thirdly, the "obvious to try" standard is inapplicable given the nature of the claimed invention. In suggesting that both administering an inhibitor of the SHH-signalling pathway and administering a GnRH agonist were known for treatment of prostate cancer, the PTO essentially suggests that it would have been obvious to try these two known treatments to achieve an additive effect. This is improper.

The Board of Patent Appeals and Interferences, citing the Supreme Court decision in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385, 1394, 1396

(2007), noted that the "obvious to try" standard *may* be an appropriate basis only when there is motivation to solve a problem and there are a finite number of identified, predictable solutions. *Ex parte Kubin,* No. 2007-0819, 2007 WL 2070495 (B.P.A.I. May 31, 2007).

In this case, both of these factors are missing. As noted above, there is no recognition in the cited art as to the nature of the problem to be solved. Moreover, this case is far from the factual situation where a finite number of identified, predictable solutions to the problem exist. In particular, Dudek I relates to the treatment of a very wide range of diseases. For example, page 14, lines 15 to 26 discloses that the method of the Dudek I invention has therapeutic and cosmetic applications ranging from regulation of neural tissues, bone and cartilage formation and repair, regulation of spermatogenesis, regulation of smooth muscle, regulation of lung, liver and tissue of other organs arising from the primitive gut, regulation of hematopoietic function, regulation of skin and hair growth, etc. Also, even with respect to the treatment of cancer, numerous cancers are disclosed including many carcinomas and papillomas (page 16, lines 9 to 29). Furthermore, numerous other diseases are mentioned including periodontal disease, dermal skin ulcers including diabetic ulcers, venous stasis ulcers and arterial ulcers, and so on (page 17, lines 6 to 16). There is no suggestion given in Dudek I (or, indeed, in Walsh) to consider combination therapy.

Under these facts, the person of ordinary skill would not have had any expectation that a GnRH agonist could be used to avoid possible adverse effects caused by a treatment involving inhibition of the SHH-signalling pathway.

For all these reasons, the rejection of claims 1 and 24-29 for obviousness over Dudek I in view of Walsh is improper and should be withdrawn.

The rejection of claims 2-8, 18, 19, and 21 under 35 U.S.C. § 103(a) for obviousness over Walsh in view of Dudek I and further in view of U.S. Patent No. 6,291,516 to Dudek *et al.* ("Dudek II") is respectfully traversed.

The teachings of Dudek I and Walsh are set forth above.

Dudek II, like Dudek I, relates to regulators of the SHH-signalling pathway and their use in treating various conditions. There is no disclosure or suggestion of using regulators of the SHH-signalling pathway in conjunction with the suppression of testosterone.

The PTO asserts at pages 26-27 of the outstanding office action that the claimed invention would have been obvious, because (i) Dudek I teaches using cyclopamine for inhibiting growth and branching of prostate cancer, (ii) Walsh teaches the use of

deslorelin for treatment of prostate cancer, (iii) Dudek II teaches the administration of cyclopamine in pharmaceutically acceptable carriers; and (iv) the combining of two compounds for a known purpose would have been expected to produce additive effects.

With regard to claims 2-8, applicant respectfully disagrees for several reasons.

Firstly, the invention of claims 2-8 relates to a method of treating a proliferative disease in a male patient, where the proliferative disease is a cancer in which SHH-signalling plays a role in its growth and/or differentiation, which cancer is *not* prostate cancer, and the method includes both inhibiting the SHH-signalling pathway and suppressing testosterone or its effect in the male patient. There is no suggestion in Dudek I that inhibitors of the SHH-signalling pathway cause adverse effects on the prostate when testosterone is present. Therefore, there is no motivation whatsoever in Dudek I to suppress testosterone, and so the skilled person would not have considered combining Dudek I with Walsh for treating cancers within the scope of the claims. Dudek II fails to overcome this deficiency.

Secondly, the fundamental premise cited by the PTO at pages 26-27—that the claimed combination is used for the same purpose—is improper. As noted above, the two steps of the invention (of claim 2) serve different purposes in the combination therapy, one to treat the proliferative disease (other than prostate cancer) and the other to avoid possible adverse effects on the prostate that may be caused by the treatment of the proliferative disorder.

Thirdly, the "obvious to try" standard is inapplicable given the nature of the claimed invention. In suggesting that both administering an inhibitor of the SHH-signalling pathway and administering a GnRH agonist were known for treatment of prostate cancer, the PTO essentially suggests that it would have been obvious to try these two known treatments to achieve an additive effect. This is improper for the reasons noted above in relation to the rejection of claim 1 over the combination of Walsh and Dudek I—namely, the PTO has failed to establish that the requisite facts exist for asserting that the invention would have been obvious to try. Moreover, as noted above, the claimed subject matter no longer reads on the treatment of prostate cancer. Thus, even if the "obvious to try" standard did apply for treatment of prostate cancer (which applicant does not admit), the PTO has failed to demonstrate that this conclusion would be appropriate for treatment of cancers other than prostate cancer in which SHH-signalling plays a role in its growth and/or differentiation.

Claims 18, 19, and 21 are directed, respectively, to a therapeutic system, composition, and pharmaceutical composition that include, *inter alia*, an inhibitor of the

SHH-signalling pathway and a compound which suppresses testosterone or its effects in a patient. Applicant submits that the combination of Dudek I, Walsh, and Dudek II are deficient and would not have rendered the claimed subject matter obvious.

The PTO has failed to assert a rationale why someone of skill in the art would have expected two known compounds to yield an additive effect. This is a baseless assertion. Even assuming for the sake of argument that one of skill in the art would have expected an additive effect (which applicant does not admit), the present application makes it abundantly clear that the compound which suppresses testosterone or its effect functions *not* in an additive manner, but instead as a protectant against possible harm caused by the inhibitor of the SHH-signalling pathway. This is neither contemplated nor expected from the prior art. These unexpected results, therefore, demonstrate non-obviousness of the claimed products.

For all these reasons, the rejection of claims 2-8, 18, 19, and 21 for obviousness over Dudek I in view of Walsh and Dudek II is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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/Edwin V. Merkel/
Edwin V. Merkel
Registration No. 40,087

NIXON PEABODY LLP
1100 Clinton Square
Rochester, New York 14604
Telephone: (585) 263-1128
Facsimile: (585) 263-1600